GEORGIA INSTITUTE OF TECHNOLOGY OFFICE OF CONTRACT ADMINISTRATION

PROJECT ADMINISTRATION DATA SHEET

[x] ORIGINAL [ ] REVISION NO. _____

Project No. G-33-R01 DATE 11/19/81

Project Director: Dr. D. S. Caine School/~~Lab~~ Chemistry

Sponsor: DHEW/PHS/NIH - National Cancer Institute

Type Agreement: Grant No. 1-R01-CA28355-01A1

Award Period: From 9/30/81 To 6/30/82 (Performance) 9/30/82 (Reports)

Sponsor Amount: $35,055 Contracted through: ~~GTRI~~/GIT

Cost Sharing: $1,845

Title: The Synthesis of Antileukemic Terpenoids

ADMINISTRATIVE DATA OCA Contact Don S. Hasty x 4820

1) Sponsor Technical Contact:

Program Official:
Dr. Moreshnar V. Nadkarni
Division of Cancer Treatment
National Cancer Institute

Phone: (301) 427-8706

2) Sponsor Admin/Contractual Matters:

Grants Management Specialist:
Ms. Margaret Learmouth
Grants Management Office
National Cancer Institute

Phone: (301) 496-7227

Defense Priority Rating: N/A Security Classification: N/A

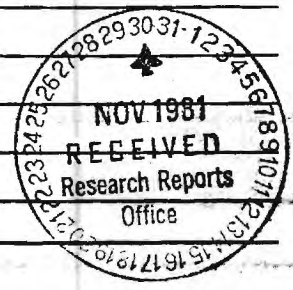
RESTRICTIONS

See Attached NIH Supplemental Information Sheet for Additional Requirements.

Travel: Foreign travel must have prior approval – Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of $500 or 125% of approved proposal budget category.

Equipment: Title vests with GIT. We are accountable for all equipment purchased.

COMMENTS:



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Project File
Other _____

FORM OCA 4:781

GEORGIA INSTITUTE OF TECHNOLOGY OFFICE OF CONTRACT ADMINISTRATION

SPONSORED PROJECT TERMINATION SHEET

Date 7/11/83

Project Title: The Synthesis of Antileukemic Terpenoids

Project No: G-33-R01

Project Director: Dr. D. S. Caine

Sponsor: DHEW/PHS/NIH - National Cancer Institute

Effective Termination Date: 6/30/82

Clearance of Accounting Charges: 9/30/82

Grant/Contract Closeout Actions Remaining:

NONE

- ☐ **Final Invoice and Closing Documents**
- ☐ **Final Fiscal Report**
- ☐ Final Report of Inventions
- ☐ Govt. Property Inventory & Related Certificate
- ☐ Classified Material Certificate
- ☐ Other _____

NOTE: Follow-on project (02 year) - G-33-R02

Assigned to: Chemistry (School/Laboratory)

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FORM OCA 10:781

APPLICANT: REPEAT GRANT NUMBER SHOWN ON PAGE 1	GRANT NUMBER
SECTION IV—SUMMARY PROGRESS REPORT	1 R01 CA 28355-02

PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last, First, Initial)	PERIOD COVERED BY THIS REPORT	
Caine, Drury S. III	FROM	THROUGH
NAME OF ORGANIZATION	09-30-81	02-28-82
Georgia Institute of Technology		

TITLE (Repeat title shown in Item 1 on first page)
The Synthesis of Antileukemic Terpenoids

1. List all publications, not previously reported, resulting from work supported by this grant (author(s), title, page numbers, year, journal or book). List manuscripts separately as submitted for publication or accepted for publication.
2. Provide two reprints of publications not previously submitted to the awarding unit.
3. Progress Report. (See instructions)

Final Report
G-33-R01 / Caine

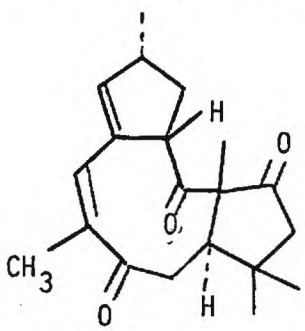
1. None

2. N/A

3. Progress Report:

1. No change

2. Our proposed approach to dl-jatrophatrione (1) involves the use of a retroaldol reaction to convert a 5/5/6/5-fused tetracyclic β-hydroxy-α-phenylsulfinyl ketone (cf. 2) into a 5/9/5-fused tricyclic enolate intermediate which can be trapped with methyl iodide and by sulfoxide elimination elaborated to the enedione system (cf. 3) of the natural product.



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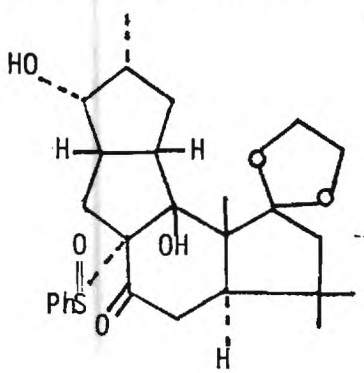

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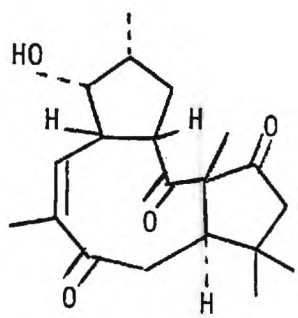
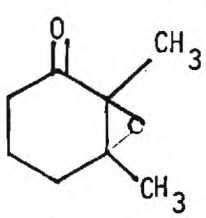


3

Initial work on the project has involved the synthesis of model compounds related to 2 and investigation of reaction conditions to effect the retroaldol-alkylation transformation. The monocyclic epoxy ketone 4, and the 5/6- and 6/6-fused bicyclic compounds 5 and 6 have been prepared by treating the corresponding enones with basic hydrogen peroxide.



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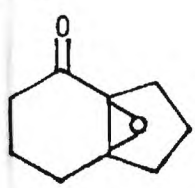

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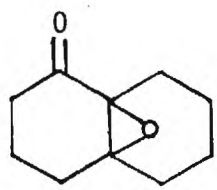
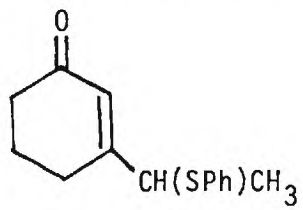


6

Treatment of epoxy ketone 4 with sodium thiophenoxide in tetrahydrofuran (THF) at 25° gave the cyclohexenone derivative 7 rather than expected β-hydroxy-α-phenylthio ketone 8α. The proposed pathway for the conversion of 4 into 7 is

shown in Scheme 1. However, when 4 was treated with thiophenol in THF in the presence of triethylamine, under the conditions reported by Silverman[1] for cleavage of an epoxy diketone related to vitamin K epoxide reductase, 8a was obtained in excellent yield. Addition of 8a to a mixture of sodium hydride and methyliodide in THF at 0° gave the keto α-phenylthio ketone 9a in greater than 50% yield. Oxidation of 9a to the corresponding sulfoxide 9b followed by heating in carbon tetrachloride gave the acyclic enedione 10 again in good yield. This method provides a useful route to diketones with chemically differentiated carbonyl groups. The behavior of 8a in the presence of other bases and alkylating agents as well as the corresponding reactions of the sulfoxide 8b, obtained by oxidation of 8a with m-chloroperbenzoic acid (MCPA), will also be explored.



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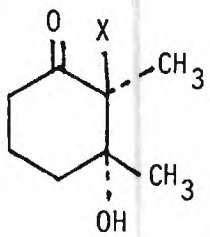
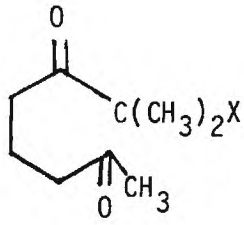
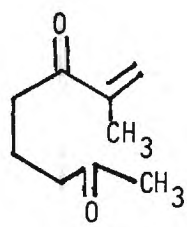


8a. X=SPh
b. X=S(O)Ph

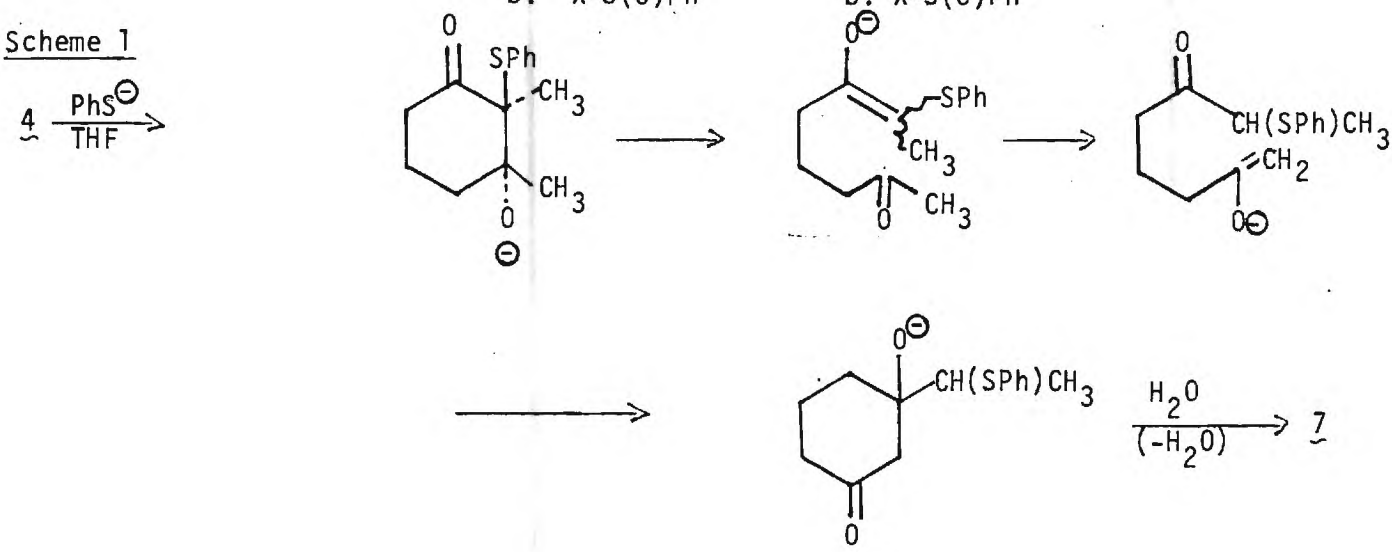


9a. X=SPh
b. X=S(O)Ph



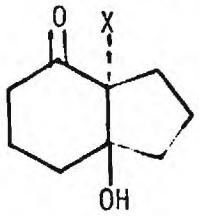
10

Scheme 1

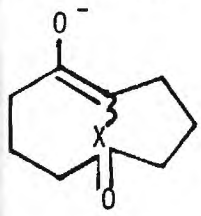


Treatment of epoxy ketone 5[2] with sodium thiophenoxide or thiophenol and triethylamine gave the trans β-hydoxy-α-phenylthio ketone 11a. Treatment of 11a as described for 8a apparently did not lead to retroaldol reaction to the monocyclic enolate 12a since a mixture of O- and C-alkylated bicyclic products were the only compounds isolated in this case.

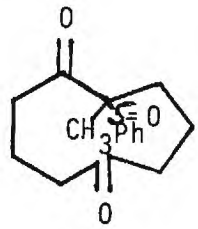
After oxidation of 11a to 11b a series of experiments were performed in an effort to generate and methylate the monocyclic enolate 12b in order to obtain the α-methyl-α-phenylsulfinyl nonandione 13. When



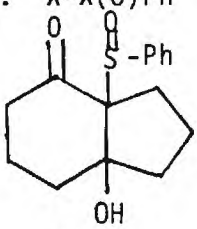
11a. X=SPh
b. X=X(O)Ph



12a. X=SPh
b. X=S(O)Ph



13



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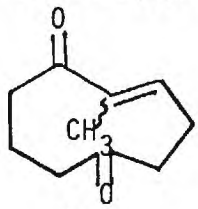
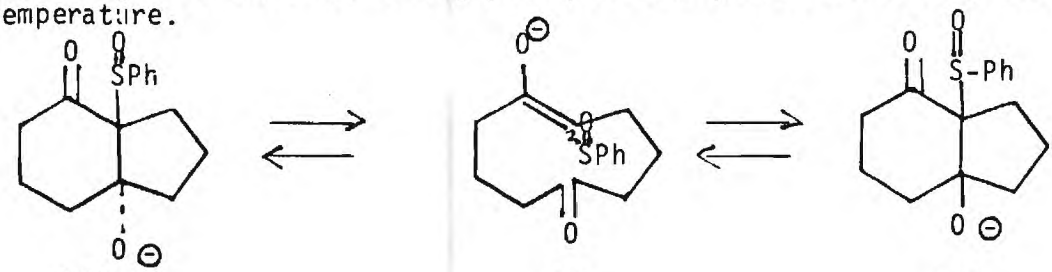


15

11b was added to a mixture of 1 equiv. sodium hydride and methyl iodide in THF or to sodium hydride in THF followed by the addition of methyl iodide, a relatively insoluble material with spectral properties (ir,nmr) consistent with those expected for the cis β-hydroxy-α-phenylsulfinyl ketone 14 was obtained. However, in a run in which 11b was added to 1 equiv. of potassium hydride in THF containing 4 equiv. of HMPA, the mixture stirred until the evolution of hydrogen ceased, and then treated with excess methyl iodide, the major product (~30% by TLC), which was isolated relatively pure by preparative TLC, exhibited spectral properties consistent with those expected for the nonandione 13 (probably as a mixture of diastereoisomers). Efforts to improve the yield of this compound and to convert it into the enedione 15 are in progress.

The available experimental results suggest that the anion derived from deprotonation of 11b exists as an equilibrium mixture containing the trans and cis bicyclic alkoxides 16A and 16C and ring opened enolate 16B. Under conditions where the cation is not strongly solvated ($Na^{\oplus}$, THF) the cis structure 16C is apparently preferred because a relatively stable six-membered ring chelate involving the metal cation and the alkoxide and sulfoxide oxygen atoms can exist. However, when the cation is strongly solvated ($K^{\oplus}$, HMPA) the ring opened α-phenylsulfinyl enolate 16B appears to increase in concentration. We hope to increase the concentration of 16B to a greater extent by increasing the polarity of the medium, using 18-crown-6 to strongly complex the potassium cation, and/or changing the temperature.

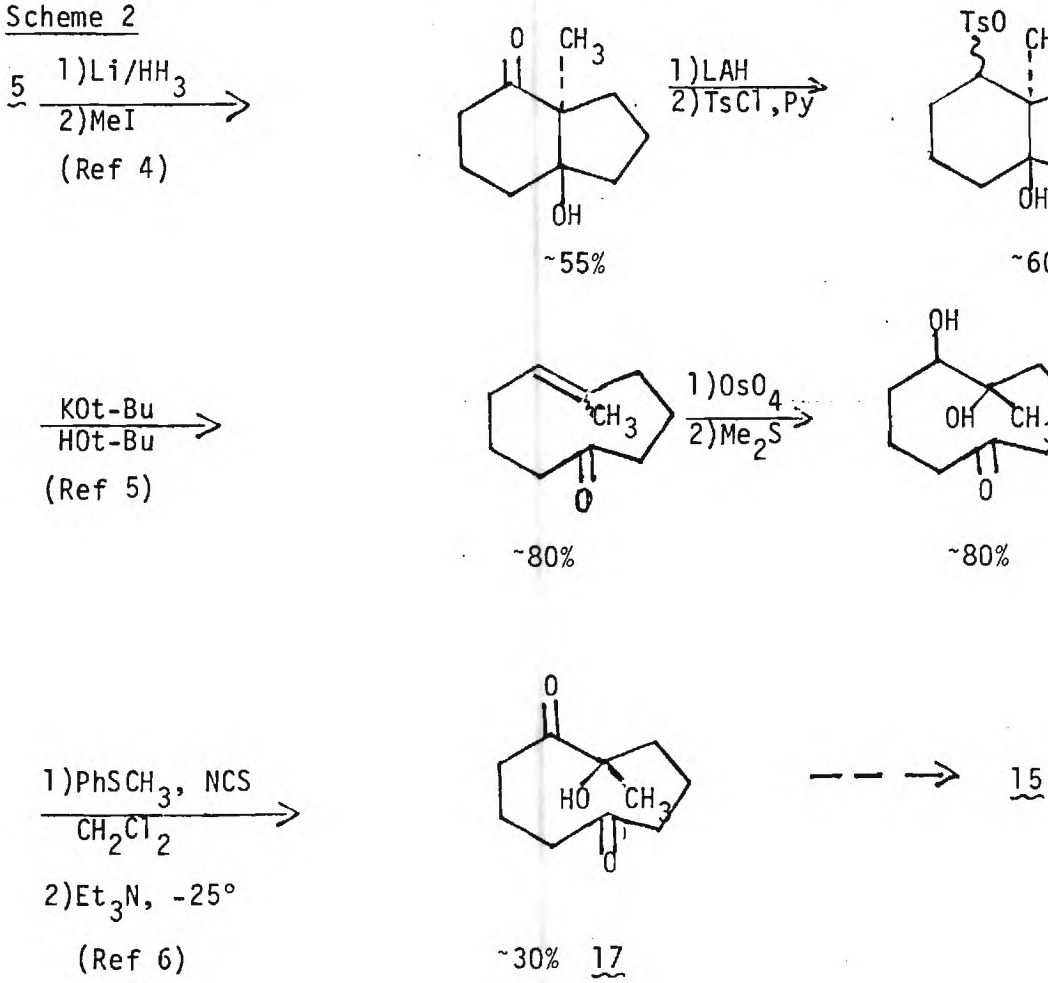


16A 16B 16C

The results of Trost[3] indicate that systems of the type 11 have a strong tendency to exist in the bicyclic form since the strain energy should increase in going from the 6/5-fused to the nine-membered ring structure. However, in the system Trost studied ring opening would have led to a phenylsulfonyl stablized carbanion whereas in the present case the formation of a relatively stable β-keto sulfoxide enolate may offset the increase in the stain energy that attends the ring opening. A comparison of the behavior of the β-hydroxy-α-phenylsulfinyl ketone derived from thiophenoxide opening of the 6/6-fused epoxy ketone 6 with that of compound 11b under retroaldol-alkylation conditions will also be made.

As shown in Scheme 2 an alternative, although more lengthy, approach for the conversion of the epoxy ketone 5 into the nonendione 15 is also under investigation. This work has progressed to the stage of the preparation of the α-hydroxy diketone 17 which should be convertible into the enedione by dehydration with thionyl chloride in pyridine. The indicated yields are only approximate at this time.

Scheme 2



References

1. Silverman, R.B. J. Am. Chem. Soc., 1981, 103 5939; J. Org. Chem., 1981, 46, 4789.

2. Lange, G.L.; Hall, T.W. J. Org. Chem., 1974, 39, 3819.

3. Trost, B.M.; Vincent, J. E. J. Am. Chem. Soc., 1980, 102, 5680.

4. McChesney, J.D.; Wycpalek, A.E. J.C.S. Chem. Commun., 1971, 542; Szajewski, R.P. J. Org. Chem., 1978, 43, 1819.

5. Wharton, P.S. J. Org. Chem., 1961, 26, 4781; Wharton, P.S.; Hiegel, G.A. ibid, 1965, 30, 3254; Corey, E.J.; Mitra, R.B.; Uda, H. J. Am. Chem. Soc., 1964, 86, 485; Tanabe, M.; Crowe, D.T. Tetrahedron Lett, 1974, 287.

6. Corey, E.J.; Kim, C.V. Tetrahedron Lett., 1974, 287.

3. During the next budget period we hope to (1) complete the studies on the use of the retroaldol-alkylation-elimination sequence to generate a nonendione system, (2) synthesize the diene and dienophile intermediates necessary for construction of the 5/5/6/5-fused system and (3) carry out the Diels-alder reaction between these components to generate the precursor of 1. As soon as appropriate tetracyclic compounds (cf. 2) become available, we expect to apply the knowledge we have acquired from model studies on the retroaldol clevage to the synthesis of a tricyclic precusor of jatrophatrione. Simulaneously, a fragmentation approach analogous to that shown in Scheme 2 will be investigated.